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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,803	02/05/2001	Vanitha Ramakrishnan	044481-5044	3916

7590 06/16/2003

Intellectual Property Group
MILLENNIUM PHARMACEUTICALS, INC.
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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,803	RAMAKRISHNAN ET AL.	
	Examin r	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,8,10,13,15,21,23,24,26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *31 March 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/31/03 has been entered.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, 26-30 are pending.

Applicants' traversal, the amendment to claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26, the addition of claims 28-30 and the cancellation of claims 2, 4, 6, 7, 9, 11, 12, 14, 16-20, 22 and 25 in paper no. 18 filed on 3/31/03 is acknowledged and considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification recites that the invention features a genus of transgenic mice comprising either a non-functional GPV gene or a modified GPV gene and goes on to contemplate that there are techniques for producing the transgenic mice (pages 5-13). The specification requires that the starting material, which is a nucleic acid encoding a GPV polypeptide, be used in a method of making a transgenic non-human mammal comprising either a modified or a non-functional GPV gene. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (page 12). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) The DNA sequence encoding GPV comprising a coding region of mouse GPV (including the putative initiator Met to Leu^{389}) was replaced by a neo cassette and injected the vector into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the disclosure provides characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the specification displays the GP V-/- mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (page 23-24). The specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (pages 25).

However, the art of record teaches a GPV-deficient mouse whose platelets have undiminished thrombin responsiveness and does not exhibit a Bernard-Soulier phenotype (Kahn et al., page 4112, cited on a previous PTO-892). Kahn produces GPV-deficient mice using gene targeting, wherein the entire GPV gene was knock out. The mice responded normally to thrombin and the tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115). The platelets from GPV-deficient mice responded to 1nmol/L thrombin like wild type mouse (page 4115). In addition, the art of record for GP V teaches that the role of GP V is poorly defined (IDS, Dong, pages 4355 and 4362).

In view of the claims lacking essential materials and methods (e.g., targeting construct used, a phenotype for the claimed mouse), one skilled in the art would not be enabled to produce a transgenic mouse as set forth in the claimed invention without an undue amount of experimentation because the claims do not distinguish the mouse taught by Kahn and the mouse taught by the specification. The conflicting phenotypes displays that the art of transgenic is not predictable art with respect to modifying a gene in a mouse and reasonably predicting the resulting phenotype from the modification. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mouse comprising a modified gene (e.g. GPV gene), it is not predictable if the modified gene would result in a particular phenotype. [Note that although the claimed transgenic mouse is not limited to modified expression of the GPV protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given

their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mouse having cells, which has a modified GP V protein, wherein the modified protein demonstrates a reduced functionality to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mouse would serve if the reduced functionality is not at a sufficient level for a resulting phenotype).]

In conclusion, in view of In Re Wands Factors, the claimed invention is not considered enabled. Furthermore, without reciting the essential materials and methods, in particular when the modification of the GP V gene must occur at a level resulting in a corresponding phenotype that would distinguished it from the mouse taught by Khan; the unpredictability of the art with respect to modified gene behavior in transgenic mouse; and the breadth of the claims drawn to any transgenic mouse whose genome has a modified GPV gene, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

Applicant's arguments with respect to claims 1, 3, 5, 8, 10, 13, 15, 21, 23, 24, and 26-30 have been considered but are moot in view of the new ground(s) of rejection. In view of the In Re Wands Factors, the specification fails to provide sufficient guidance or factual evidence for one skilled in the art to practice the claimed invention. The interpretation of the claimed transgenic mouse having cells, which has a modified GP V protein, wherein the mouse does not express a functional GP V protein compared to the GP V protein of a wild type mouse to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mouse would serve if the reduced functionality is not at a sufficient level for a resulting phenotype). Thus, the specification does not provide sufficient guidance for how to use the claimed invention.

Furthermore, in view of the conflicting phenotypes of a GPV deficient mouse taught by the specification and the art of record, the specification fails to provide sufficient guidance and/or factual evidence for how to distinguish between operable and inoperable embodiments embrace by the claimed invention, e.g., how to use the GPV deficient mouse taught by Kahn in the claimed invention.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment…; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d…[1557], 1562, 27 USPQ2d…[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using a transgenic mouse whose genome comprises a modified GP V, for those skilled in the art to experiment with level of expression so as to provide a transgenic mouse as intended by the as-filed specification at the time the invention was made.

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for a transgenic mouse whose genome comprises a non-functional GP V protein or expresses a GPV protein which demonstrates reduced functionality as compared with wild type GPV protein, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from a

GPV deficient mouse with no phenotype to practicing the claimed invention. Therefore, the as-filed specification is not enabled for the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5, 8, 10, 23, 24, 26, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moreadith et al. (J. Mol. Med. 75:208-216, 1997) taken with Dong (IDS, Blood 89:4355-4363, 1997) in further view of Ravanat et al. (Blood, 89: 3253-3262, 1997).

Moreadith teaches making and using knockout mice to gain insight into the function of a gene (pages 211-212). Moreadith further teaches the components of a targeting vector and the steps involved for targeted gene replacement in ES cells (pages 210-212). Moreadith further teaches using the ES cells to produce knockout mice. However, Moreadith does not specifically teach making and using a knockout mouse whose genome comprises a modified glycoprotein V (GP V) gene, wherein said gene has been modified so that the mouse does not express a functional GP V protein or expresses a GPV protein which demonstrates a reduced functionality a compared with the native or wild type GPV protein.

However, at the time the invention was made, Dong teaches inserting the gene for GP V into *in vitro* cells and characterizing the GP V gene as well as its function with regard to the platelet high-affinity thrombin receptor (page 4356). Dong further teaches that platelets were used in studies to determine the role of GP Ib-IX-V complex in thrombin action (page 4355). Note that absent any phenotypic requirements of the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention.

In addition, at the time the invention was made, Ravanat teaches gene cloning of the rat and mouse platelet GP V gene (pages 3254-3256).

Accordingly, in view of the teaching of Dong and Ravanat, it would have been obvious for one of ordinary skill in the art, at the time the invention was made, to modify the knockout technology of Moreadith by use of a targeting vector for disruption of the known GP V gene in a

mouse with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse, and particularly since Dong discloses a correlation between GP V and formation of the platelet high affinity- binding site. In addition, one of ordinary skill in the art would have been motivated to use platelets from the knockout mouse to study the role of GPV in the GP Ib-IX-V complex in thrombin action.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicant's arguments with respect to claims 1, 2, 5, 8, 10, 13, 23, 24, 26, and 27 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1635